

Panel on Arteriosclerosis*

WILLIAM DOCK, MODERATOR

Dr. William Dock (professor of medicine, Downstate Medical Center, State University of New York): One of the points I should like to make, is that smoking acts on the circulation only by the absorption of nicotine. It has nothing to do with the smoke. In other words, to get on the wrong side of the cook-out fire will not increase much the risk of coronary disease, although it might give you bronchial carcinoma after 50 or 100 years. Nicotine acts much as though the individual who smokes a cigarette or gets a good chew of tobacco had been given a good intravenous infusion of epinephrine or norepinephrine. The free fatty acid goes up, the blood pressure goes up, and the stroke volume goes up. The stresses produced on the circulation by nicotine are exactly like those produced by catecholamines. While you can change to chewing or switch to a pipe to get rid of obstructive emphysema, the effects of nicotine on the coronary vessels will be the same no matter how you absorb it. We assume the effects of smoking on coronary disease are what you'd expect if the patient were getting infusions of epinephrine during the day, at regular and very frequent intervals. Caffeine also apparently acts in somewhat the same way. Of course, Coca-Cola does, too. Any of these things can accelerate atherosclerosis some. As the people in Cincinnati have reported repeatedly, and as the nicotine symposium held in New York at the National Academy of Sciences strongly emphasized, chewers of tobacco have much worse vascular disease in the legs and much more coronary disease, age corrected, than two-pack-a-day cigarette smokers. Of course, they get

the most nicotine for their money. If you want nicotine, and they want nicotine, there is a price to pay when you are on the North American diet. On the other hand, presumably, a tobacco smoker in North China runs no additional risk of coronary disease, because he runs no risk to begin with.

Dr. William Hollander (associate professor of medicine, Boston University School of Medicine): Dr. Dock, could I perhaps comment on the effect of catecholamines on the metabolism of the arterial wall? We have some observations regarding the effects of norepinephrine on our incubated arterial tissue, including atherosclerotic tissue. What we have been finding is that, as you have indicated, catecholamines stimulate the lipoprotein lipase activity in atherosclerotic tissue. Consequently, the triglyceride content falls off very strikingly within a period of four hours. You can actually measure a drop in the lipid content in these arterial walls.

What about Buerger's disease? This disease can be aggravated by smoking. I do not know what the *in vivo* effects of norepinephrine are in Buerger's. And anyway, in Boston the pathologists say that there is no difference between Buerger's disease and ordinary atherosclerotic disease of the legs.

Sir George W. Pickering (regius professor of medicine, Oxford University): Could I disagree with that? I have been concerned with people with vascular disease of the legs ever since I went to work with Sir Thomas Lewis. These two diseases are quite different clinically, whatever they are like histologically. Buerger's disease is a disease of young men which is practically unknown in females, and it stops like that if you stop smoking. The influence of tobacco on Buerger's disease is, I think, 100%.

Dr. Dock: Early Buerger's arteries are full of lipid only with the North

American diet of the present time. When you get syphilis, or when you get Buerger's disease, you get atherosclerosis on top of it because of our diet. In the regions where people don't get highly fatty diets you can see pure Buerger's, and you can see pure syphilitic aortitis without atheroma.

Well, we don't want any of our patients to get syphilis and we hope they all will stop smoking. The smoking influence is so clear-cut in statistical studies that it is a tragedy that it is easier for a patient to have blood drawn every week to see how his prothrombin is doing, and take Coumadin pills, than it is for him to stop buying tobacco. Tobacco is an extremely addicting drug, probably as addicting as morphine. And the physiological damage done by tobacco or nicotine is certainly much worse than that done by morphine. If you don't smoke opium, you don't get obstructive emphysema from it. If you take morphine in little pills, it makes you feel good just the way smoking does, but it does not produce the catecholamine effect, and there is no evidence that it produces arteriosclerosis or even aggravates it. So, we are hoping to get the Narcotic Act repealed! Everybody on the panel but me and Dr. Stamler, I think, are two-pack-a-day or nine-pipe-a-day smokers. You see how hard it is to stop the addiction. Dr. Pickering and I knew three full professors of medicine in leading American universities who died of obstructive emphysema. Not one of these men could cut down his smoking though he knew he was headed for the boneyard. One of them used to sneak into his garret and smoke so his wife could not catch him, and this was after he had been in the hospital and in a helium tent. So, we have agreed on the panel that you cannot give up smoking, and most of us agree, I think, that patients cannot be persuaded to stay on diets. Dr. Stam-

* Held during the Thirty-sixth annual McGuire Symposium on Hypertension and Arteriosclerosis, Medical College of Virginia, October 7-9, 1964.

ler, can they be persuaded?

Dr. Jeremiah Stamler (director of the heart disease control program, City of Chicago Board of Health): The question is not whether people can be persuaded to stay on a diet. I think the question is whether a population can change its eating habits sufficiently to alter the pattern of a disease. If what we are really talking about is meaningful and important, it has a whole lot of sociological consequences which come into play beginning with the earliest period of habit formation, in the time of weaning. I was talking with Dr. William Harlan about what happens to young men in America. They are very active in athletics, they develop the training table or the basic training pattern of eating. Then they stop physical activity when they cease to be active in athletics or leave the armed forces, but they keep on eating the same way. Or, even worse, they fall into the hands of a wonderful, lovely little girl who wants to show that she learned the right things from Mamma about cooking.

Dr. Dock: Now, Dr. Pickering, I think we should give you a chance to get back into the argument. In the first place, does your group feel that diet has any importance whatever in the pathogenesis of vascular disease?

Prof. Pickering: As August Krogh once remarked, "Physiological phenomena are so complicated that, if you argue from more than one step to another without the control of experiment, you are almost certain to go wrong." Before I would be prepared to encourage a mass change of diet, I would like to have a pilot study to see that this mass change was doing a certain amount of good. If I remember rightly, there is a certain well-known professor of medicine who put himself on a very rigid low-fat, no cholesterol diet, and has since had a cholesterol stone removed from his gall bladder.

Dr. Dock: And you conclude that it formed after he went on the diet?

Prof. Pickering: Well, he may have had it before, that is perfectly true.

Dr. Dock: I think that Dr. Pickering has brought up a very important point. A man with asymptomatic gall stones who goes on a diet with vegetable oil is very likely to have his stones decrease in size to where they can slip

into the cystic or common duct. Then he will have his first attack of colic one, two, or three years after he has cut his cholesterol intake, because the stones will get smaller and give symptoms. I have had three such patients. One of them had his gall stones taken out at Peter Bent Brigham Hospital after his fifth attack of colic. His first attack came on about three years after he changed his diet. Fortunately he had had his gall bladder visualized eight years before, and beautiful, big cholesterol stones had been seen, far too big to get into his duct.

I think that if you try to starve too fast, you may run your serum triglycerides up quite high by starvation. People have their first bout of myocardial infarction just after they have gone on a marked weight reduction program. This has been noted over and over again. There is a great craze now in parts of the United States for starvation as the way to start a weight reduction program. It can be predicted that this should up the incidence of coronary disease in the first three months after you go on that sort of program. Whether it will, I don't know.

I think that physicians who feel, as Dr. Pickering and his group do, that the role of diet in vascular disease is not yet established, should say as much to their patients. This seems to me to be perfectly sound, rational management.

On the other hand, Pickering is a doctor who thinks perhaps Harvey was right in saying that if animal experiment indicates that the blood circulates, then it may circulate in man. If you take animal experiment as being relevant to human physiology and pathology, and you know that dietary manipulation will produce vascular disease in chickens, rats, guinea pigs, rabbits, dogs, hamsters, monkeys, and pigs, it does become a little awkward to say, "Well, we don't believe that animal experiment is relevant to human experience in this particular field." It is perfectly sound doctrine to say this, as it was for Dr. Sydenham to say, "Just because Harvey thought that blood circulated in a snake or a deer is no reason to think that blood circulates in man." To me, this is perfectly sound, rational argument. Sydenham

was the greatest internist of his generation. You can be a great man in your generation, and it may turn out that you were right. Or, it may turn out that you did not take as seriously as you should have the data that were available.

Prof. Pickering: Yes, there is a little difference, though. You will recall that Krogh said, "If you argue from one set of data to another without the control of experiment you are likely to go wrong." And I believe that there is a difference between the rabbit and the human being. The diet that rabbits eat in experiments is very different from the diets that they ordinarily eat. And the lesion which is produced in rabbits is not quite the same as the lesion which produces myocardial infarction in men. And so, I think your reasoning will not hold up at every point, and even if it did, man is a different species from rabbit. I would like to see the effect of diet demonstrated in man before I am prepared to believe it is effective in controlling vascular disease.

Dr. Dock: Well, this experiment is under way in the United States at enormous expense at the present time.

Dr. Stamler: Could I just say a word about this? I didn't get to hear Sir George, but I have read some of his writings, and I had the good fortune to hear the tape of his lecture earlier in this symposium. I'd like to dismiss one or two of the arguments which I don't think are entirely valid, or, if not dismiss them, at least put them on the table for rediscussion. The first is the question of the rabbit as an atypical species. The second is the matter of drowning the animals in very high cholesterol, high fat diets. Both of these were problems in 1948. I do not think either is much of a problem now for the following reasons: 1) The disease has, in fact, been reproduced, with a lesion remarkably similar to the human lesions, in a wide range of species, as Dr. Dock said. So the problem that did confront workers in the 1930's, that of the ability to reproduce the disease only in the rabbit or guinea pig, is no longer entirely true. In fact, quite the opposite is true. We have the dog, rat, chicken, rabbit, and a variety of monkeys. The monkey experiments have been done using diets similar to the human diet, in fact, feeding human

foods in periods that correspond to a life span equivalent to human beings. These produced moderate elevations of the serum cholesterol level in the 200's and 300's, peripheral gangrene, myocardial infarction, and cerebral infarction.

On the question of experiment in man, I would like to add a word to that. As practicing doctors, I think that the profession has a very difficult problem. Let's face it, these studies in the population may not come off. If they do come off, they will take a decade at least to get an answer. And what does one do in the interim, wait for the results of the experiment, and say, "Well, we're not sure." That's OK, but every physician who makes that decision has to accept the corollary of it, and even has to tell his patient of the corollary. "If you are a high risk, middle-aged American man, I have very little to offer you while I'm waiting for the purity of a scientific answer." Because, really, we do not have much to offer aside from our approach to these risk factors, of which diet, blood cholesterol, and weight are three key ones. If we are prepared to accept that corollary, and transmit it to our patients, then I say we can wait for the big experiment, if it ever gets done. If not, I think we should intervene in a safe way.

Prof. Pickering: Well, that is what I think I said. If the doctor, himself, does not believe in this, he should tell his patients he does not believe in it. If they want to go on the diet, he is glad to direct them. If he does believe in it, he has got to practice what is known as the Golden Rule and say, "If I had your trouble, this is what I would do. . . ." I think this is the best any of us can do. The same thing applies to the use of anticoagulants. If the patient says, "Well, would you take this yourself?" I have to tell him that I hate to have my arms stuck every week, and for a difference in mortality of 4% as against 5% a year, roughly, I don't believe I would take all of this trouble.

Dr. Stamler and I have rather different views about atherosclerosis, I think. He would include a lot of lesions that I suspect are not the same.

Dr. Stamler: I include only lesions with porridge in them—no lipid, no

atherosclerosis, as far as I am concerned. Patients who have been starved have fibrous plaques and calcium, but no demonstrable lipid when they die. It is true in man that the lipid can disappear so you see only the scar of the disease. If I had to limit the diagnosis of syphilitic aortitis to people in whom I could demonstrate treponemes, I would be out of luck, because penicillin has killed the treponemes in all of my patients. Just as I diagnose former syphilitic aortitis from sections, I now diagnose former atherosclerosis at autopsy in patients who, as a result of leukemia, say, have lost a great deal of weight and been markedly undernourished through periods of about two years before they died. So you can lose the lipid from plaques, I'm sure. Furthermore, I believe that lipid is present in the lesions of adolescence in larger quantities than it is in the lesions of men of 40, and is present in larger quantities in men who die at 40 than it is in men who die at 70. These are my own views. This is almost a question of religious experience. Dr. Pickering belongs to one church, and has had one religious background in this field. I belong to a different church, having had different clergymen working on me in my youth. So, I don't expect to convince Professor Pickering that the lesions I showed in small vessels are related to the lesions that the same patients had in their coronary arteries, although both of those patients from whom I showed you sections were hypertensives with hypercholesterolemia who died of myocardial infarction. They had lesions in small arteries. Dr. Pickering thinks these are unrelated to the lesions in the coronaries. I cannot see why they might not be the same lesions.

Prof. Pickering: Well, I think they are different. Partially because they look different, and partially because, in the small arteries, kidney, and in the retinal arterioles, lesions are much more closely correlated with the height of the arterial pressure than is the disease I was talking about which produces big nodules in arteries like the carotid, and ultimately leads to thrombosis of them.

I will not agree with Dr. Dock that, because you can see lipid in them both, they represent the same disease. He says we belong to different churches. I

think he does belong to a church. I am just a plain agnostic.

Dr. William R. Harlan, Jr. (director of clinical research center, Medical College of Virginia): It is much easier to make long studies of large series of cases with a drug than it is with a diet, and I think this may turn out in the end to be a more profitable way of shedding light on what the plasma lipid has to do with arteriosclerosis in man. It will not settle whether plasma lipid acts by accelerating coagulation, but at least it would cast some light on whether changing the lipid levels in the plasma would improve the prognosis.

We ought to ask Dr. Stamler about estrogens and the drug androsterone, which we produce in our bodies—a very weak androgen but it tends to lower blood cholesterol. These two agents can be given to lower plasma lipid, at least plasma cholesterol levels, in male patients. Are you still carrying on estrogen studies?

Dr. Stamler: In brief, there are three reports of a controlled nature on the estrogens in post-myocardial infarction in man. One of them is a British study by Oliver and Boyd that deals with 100 patients up to age 65. Another is an American study that deals with men of all ages on lower doses of mixed conjugated equine estrogen. Oliver and Boyd used ethanyl estradiol. The third study is by our group in Chicago, using mixed conjugated equine estrogens in men under 50. In the 100 patients whom they studied, Oliver and Boyd got completely negative results, although serum cholesterol levels were lower. The Los Angeles study with lower doses of mixed conjugated equine estrogen is still in progress, but there are positive results, particularly in the patients under 50. I think none of these studies to date permits a clean-cut decision on the efficacy of estrogens. I might note that there is a peculiar aspect to the estrogen work; while ethanyl estradiol consistently lowers total blood cholesterol level, mixed conjugated equine estrogens do not. They shift the lipoprotein pattern, but they do not consistently lower the total cholesterol level. They raise the α - and may lower the β - proportionately, so that total cholesterol changes very little. They do, unques-

tionably, convert the α - from a male level of about 50 or so to a female level of 250, 300, 350, or greater. Whether this is efficacious is, of course, moot.

Dr. Dock: One of the questions is whether a reduction in blood pressure will help us have a lower incidence of cardiovascular disease. I think you believe it will.

Prof. Pickering: No, I don't believe it will. I think the evidence suggesting this is bad.

Dr. Dock: You said that in severe hypertensives, lowering blood pressure changes the whole course of the disease. If this is true, how can it help but lower the death rate?

Prof. Pickering: Oh, I thought you were talking about arteriosclerosis.

Dr. Dock: No, no. In any sort of vascular disease, will lowering the blood pressure improve the prognosis?

Prof. Pickering: Well, it depends on how high the blood pressure is. If the blood pressure is very high, or if you get a patient in the malignant phase before the kidneys are really very severely involved, then I think the evidence is quite clear that you can prolong the expectation of life.

Dr. Dock: But in a patient with a lower level of blood pressure and with a myocardial infarct, is it worthwhile to try to lower the blood pressure?

Prof. Pickering: No, I would not say that. But I think that I have distinguished what I would regard as established, and what I would regard as a sufficient degree of probability, so that I would use it in the treatment of my patients. I do not regard it as established that diet will reduce the prevalence of myocardial infarction, but instead, I do advise my patients: 1) to try to regain their youthful figures, 2) to substitute corn oil for their ordinary cooking fat, 3) to take as much exercise as they conveniently can, 4) if their arterial pressure is high, I reduce it, and 5) if they are under 55 and male, I put them on anticoagulants, but I do not ever go very high with them, because I am afraid of them. I do not use anticoagulants in patients with peptic ulcer, gross hypertension, or liver disease.

Dr. Dock: Well, I think with this useful advice, perhaps we had better bring the meeting to a close.